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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,089	03/08/2001	David R. Phillips	MPI95-0151RCPA1DV1M	7657

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MILLENNIUM PHARMACEUTICALS, INC.
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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,089	PHILLIPS ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-23,30 and 32-44* is/are pending in the application.

4a) Of the above claim(s) *35-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23,30, 32-34, and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 21-23, 30, and 32-44 are pending.

In the election of species, filed 9/08/03, Applicant elected carcinoma as the cell type for examination.

Accordingly, Claims 35-40 stand withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to nonelected species.

Claims 21-23, 30, 32-34, and 41-44 are being acted upon.

2. Applicant's amendment and remarks, filed 4/26/05, is acknowledged. In view of Applicant's amendment, in particular the new limitation that integrin tyrosine phosphorylation is determined, the previous rejection under 35 U.S.C. 102(b) in view of Hibbs et al. (1991) has been withdrawn. Hibbs et al. found "little if any" tyrosine phosphorylation in their assay.

3. Currently pending are three separate rejections under the first paragraph of 35 U.S.C. 112 (for the introduction of new matter into the claims) necessitated by Applicant's last three amendments (1/05/04, 6/29/04, and 10/29/04). As Applicant has addressed the rejections together, for purposes of clarity, the rejections are now consolidated (with new rejections) into a single set of rejections. The rejection of each claim (for the combined reasons) will be addressed separately.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 30, 34, and 42-44 stand/are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed, for the reasons

set forth in the actions mailed 3/29/04, 8/31/04, and 1/26/05. This is a new matter rejection.

Regarding Claim 30, the claim recites a method of identifying integrin-mediated signaling in/by a cell comprising measuring tyrosine phosphorylation employing the steps of Claim 22 and, additionally, preparing the extract of Claim 22 with a high concentration of SDS.

Applicant indicates that support for the claim can be found at page 43 of the specification. At page 43 of the specification is found Example 1 wherein tyrosine phosphorylation of GPIIIa (β3) in platelets is analyzed by SDS gel disc electrophoresis. This limited disclosure cannot support the generic method of the claim. For example, the cite discloses no generic analysis of any integrin β cytoplasmic domain, nor does it teach said analysis in any cell type (indeed, platelets are not even generally considered to be cells). Further the specification fails to disclose the high concentration of SDS recited in the claim.

Regarding Claim 34, the claim recites a method of identifying integrin-mediated signaling in/by a carcinoma cell comprising measuring tyrosine phosphorylation employing the steps of Claim 22.

Applicant indicates that support for the claim can be found in Examples 4-6 of the specification. Example 4 discloses the analysis of β1 phosphorylation in the KB carcinoma cell line. Example 5 discloses the analysis of β5 phosphorylation in the M21 and FG cell lines. Example 6 discloses the analysis of β6 phosphorylation in the KB carcinoma cell line. Example 5 discloses the analysis of β6 phosphorylation in the FG-2 cell line of Busk et al. (1992). These specific disclosures cannot support the generic limitations of the claim.

Regarding Claim 42, the claim recites a method of identifying integrin-mediated signaling in/by a cell comprising measuring tyrosine phosphorylation of the specific sequences, i.e., SEQ ID NO:16, SEQ ID NO:19, SEQ ID NO:17, and SEQ ID NO:21, β3, β5, β6, and β7, respectively, employing the steps of Claim 22.

No specific support for the specific use of these sequences has been provided. Note that the Brief Description of the

Drawings indicates at page 12 that these sequences "show cytoplasmic domains of various integrin subunits", but pages 14-15 of the specification discloses that the cytoplasmic domains of the β subunits are the shorter SEQ ID NOS:1-7. As all of the sequence identifiers were added after filing, it appears impossible to establish which sequences actually represented the proper β subunits at the time of filing.

Regarding Claims 43, the claim recites a method of identifying integrin-mediated signaling comprising measuring tyrosine phosphorylation of SEQ ID NO:16 in β3.

Applicant indicates that support for this claim, and Claim 44, can be found in Example 1 and at pages 30-31 of the specification. As set forth above, Example 1 is a specific, not a generic, disclosure and cannot, thus, support a generic claim. The specification at pages 30-31 discloses only αVβ3 and GpIIb-IIIa and not the generic β3 of the claim.

Regarding Claims 44, the claim recites a method of identifying integrin-mediated signaling in/by a cell comprising measuring tyrosine phosphorylation of SEQ ID NO:16, in β3, employing the steps set forth in the claim. As set forth above, Example 1 is a specific, not a generic, disclosure and cannot, thus, support a generic claim. Also note that the example discloses a method employing platelets and not the generic cells of the claims.

6. The following are new grounds of rejection necessitated by Applicant's amendment.

7. Claims 21-23, 30, 32-34, 41, and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification,

while being enabling for, a method to identify integrin mediated signaling comprising determining whether the cytoplasmic domain of the β1 or β3 subunit of the integrin is phosphorylated on tyrosine, wherein a phosphorylated tyrosine indicates integrin-mediated signaling,

does not reasonably provide enablement for, a method to identify integrin mediated signaling comprising determining whether the cytoplasmic domain of the β subunit of the integrin is phosphorylated on tyrosine, wherein a phosphorylated tyrosine indicates integrin-mediated signaling.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

A review of the specification reveals that tyrosine phosphorylation was actually measured only on GPIIIa (β3). All other examples appear to be prophetic (though some confusing use of both past and present tenses in some of the examples is noted). The specification discloses that the cytoplasmic domains of β1, β2, β3, β5, β6, β7, and β8 are homologous, thus, the conclusion is drawn that since tyrosine phosphorylation can be used as a marker for integrin-mediated signaling in platelet GPIIIa (β3), such signaling in all β-expressing integrins can be measured similarly. However, as noted by Applicant in the instant remarks, in the CD18 (β2 integrin) subunit of Hibbs et al., integrin signaling is associated almost exclusively with serine phosphorylation. A stated by Applicant in the instant remarks, "Hibbs et al. only detected phosphorylation on serine

and threonine (page 1231, Fig. 5)". Clearly then, Applicant's logic regarding the homology of β integrins and the correlation of tyrosine phosphorylation with integrin signaling is flawed and the claimed method cannot function as a measure of integrin-mediated signaling in all β-expressing integrins. Accordingly, the generic method of the instant claims must be considered highly unpredictable and requiring of undue experimentation to practice as claimed.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 21 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sanchez-Mateos et al. (1991).

Sanchez-Mateos et al. teaches a method to identify integrin mediated signaling comprising determining whether the cytoplasmic domain of an integrin β1 subunit is phosphorylated (see particularly Abstract, Figure 7, and Discussion page 3826, column 2).

The reference clearly anticipates the claimed invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 2, 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sanchez-Mateos et al. (1991) in view of Zeromski et al. (1995), Vitale et al. (1994), and Kawahara et al. (1995).

Sanchez-Mateos et al. teaches a method to identify integrin mediated signaling comprising determining whether the cytoplasmic domain of an integrin β1 subunit is phosphorylated.

The reference further teaches that VLA integrins participate in intercellular contacts and aggregation (see particularly Abstract, Figure 7, and Discussion page 3826, column 2).

The reference teaching differs from the claimed invention only in that it does not teach involvement of an integrin subunit in carcinoma cell signaling, in particular, the β3 subunit.

Zeromski et al. teaches that VLA integrins play an important role in the interactions between lung carcinoma and its host (see particularly, Discussion, pages 66-68).

Vitale et al. teaches that VLA integrins can be associated with thyroid tumors (see particularly, the Abstract, Figure 1 and Table 1).

Kawahara et al. teaches that integrins β3 and β5 are involved with invasive gastric carcinoma (see particularly, Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method to identify integrin mediated signaling comprising determining whether the cytoplasmic domain of a VLA integrin subunit is phosphorylated, as taught by Sanchez-Mateos et al., given the teachings of Zeromski et al. that that VLA integrins play an important role in the interactions between lung carcinoma and its host, and Vitale et al. that VLA integrins can be associated with thyroid tumors. One of ordinary skill in the art would have been motivated to identify the signaling of integrins β3 and β5 in particular given the teachings of Kawahara et al. teaches integrins β3 and β5 are involved with invasive gastric carcinoma.

12. No claim is allowed.

13. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr.

Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

15. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Additionally, the Technology Center receptionist can be reached at (571) 272-1600.

7/11/05

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